

## REMARKS

Applicant respectfully requests reconsideration of the application in view of the following remarks.

Claims 1-4 and 6-14 remain pending and are not amended.

Page 3 of the Office Action states that the obviousness rejections set forth in the previous Office Action “are moot in view of new grounds of rejection.” To the extent that the previous rejections have not been withdrawn, Applicant respectfully requests reconsideration and withdrawal thereof for the reasons set forth in Applicant’s previous responses.

The Office Action sets forth new obviousness rejections, as follows:

### **1. Claims 1-3, 6-8, 10 and 11-14**

Claims 1-3, 6-8, 10 and 11-14 are rejected for alleged obviousness in view of U.S. 4,919,937 (the Mauvais-Jarvis patent), Mauvais-Jarvis, *Current Therapy in Endocrinology Metabolism* (1988), Pujol (1995) and Fentiman. Claims 1-3, 6-8, 10 and 11-14 also are rejected for alleged obviousness in view of U.S. 4,919,937 (the Mauvais-Jarvis patent), Mauvais-Jarvis, *Senologies et Pathologie* (1986), Pujol (1995) and Fentiman. Applicant respectfully traverses these rejections for the reasons set forth below.

The Office Action cites the Mauvais-Jarvis patent for teaching “a method of treating benign conditions of the breast” by applying to a breast “an aqueous alcoholic gel comprising 4-OHT.” As recognized in the Office Action, the Mauvais-Jarvis patent does not specifically mention the treatment of mastalgia, and does not teach the dosages recited in the instant claims.

The two Mauvais-Jarvis articles, *Current Therapy in Endocrinology Metabolism* (1988) and *Senologies et Pathologie* (1986), are cited for the same teachings, *i.e.*, that mastalgia may be a symptom of benign breast disease, that 4-OHT has an affinity for the estrogen receptor that is 100 times greater than that of tamoxifen, and that 4-OHT can be administered percutaneously to avoid the systemic effects of oral tamoxifen.

The Hilt Declaration submitted with Applicant's previous response evidences that the estrogen receptor binding activity of 4-OHT is "not necessarily predictive of clinical efficacy." Hilt Declaration, ¶22 (summarizing information set forth in ¶¶ 19-21). Thus, the continued reliance on the reported estrogen receptor affinity of 4-OHT to support the obviousness rejections is not supported by the record as whole, and indeed is contrary to the evidence provided in the Hilt Declaration. Moreover, as attested in the Hilt Declaration, neither of the cited Mauvais-Jarvis articles provides any basis on which the person skilled in the art reasonably could predict that 4-OHT could be used to treat mastalgia, as recited in the instant claims. Hilt Declaration, ¶¶ 27, 28.

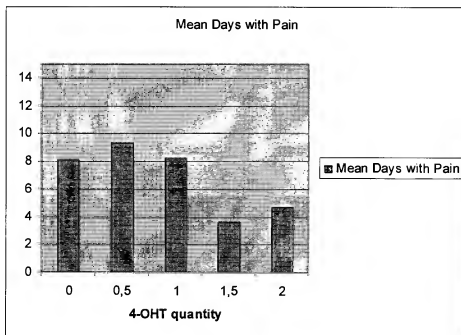
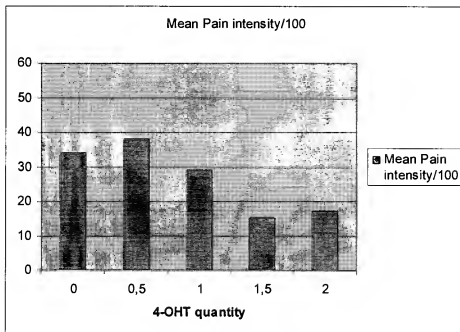
The Office Action cites Fentiman for teaching the use of oral tamoxifen to treat cyclical or non-cyclical mastalgia. The Hilt Declaration evidences that Fentiman's work with tamoxifen in no way suggests that similar results could be achieved with 4-OHT. Hilt Declaration, ¶¶ 8, 24. The Examiner's failure to take into account the evidence provided in the Hilt Declaration is contrary to MPEP § 2145, which requires Examiners to consider and give appropriate weight to all evidence of non-obviousness.

The Office Action cites Pujol for teaching the administration of "0.5 mg, 1.0 mg [and] 2.0 mg" of 4-OHT "in a hydroalcoholic gel to breast areas," but that reflects a misreading of Pujol. Pujol applied 4-OHT to breast areas, and to "a large cutaneous area excluding the breasts." Pujol, pg. 494, col. 1-2. *Pujol only applied 0.5 mg/day or 1.0 mg/day to breast areas.* Pujol, pg. 494, col. 1. (Pujol applied 1.0 mg/day or 2.0 mg/day to the large, non-breast area.) *See also*, Pujol, pg. 497, col. 2, discussing the 0.5 mg day and the 1.0 mg/day dosages. Thus, Pujol does not teach or suggest application to the breasts of the amounts of 4-OHT recited in the instant claims.

The significance of the recited amounts is underscored by the data reported in the specification, in Example 4 at pages 20-22. The reported data show that the percutaneous application of 4-OHT to breasts at doses of 0.5 mg/day or 1.0 mg/day is *not effective against mastalgia*. Thus, if the skilled artisan combined the teachings of the Mauvais-Jarvis references with Pujol, and applied up to 1.0 mg/day 4-OHT to breasts, they would conclude that 4-OHT is *not* useful for treating mastalgia. On the other hand, when a dose of at least

1.5 mg/day is applied to breasts, as recited in the claims, the results are effective, whether assessed by mean pain intensity or duration of pain.

The data reported in Example 4 is illustrated graphically below, to demonstrate the marked effect of the dosages recited in the instant claims.



There is no teaching or suggestion in the cited references that would have led the skilled artisan to combine the teachings of the Mauvais-Jarvis references with Pujol, and then modify the teachings of Pujol to arrive at the claimed invention.

The Office Actions cites *In re Aller* in support of the obviousness rejection, but that case does not apply here. Indeed, *In re Aller* applies only “where the general conditions of a claim are disclosed,” and the application at issue only provides “optimum or workable ranges by routine experimentation.” As shown above, none of the cited references directly teach that 4-OHT can be used to treat mastalgia, and none disclose a dosage range that shows any efficacy against mastalgia. It can hardly be said that the prior art discloses “the general conditions” of the invention when such a critical condition as effective dosage range is completely absent, particularly where the prior art provides absolutely no data indicating that any amount of 4-OHT would be effective to treat mastalgia, as claimed.

The basis of the obviousness rejection appears to be that the cited references would have “motivate[d] a person of ordinary skill in the art to use 4-OHT in a method of treatment of mastalgia,” *e.g.*, that it would have been “obvious to try” 4-OHT in the recited methods. Although the Supreme Court in *KSR* stated that, in some circumstances, an invention that was “obvious to try” may be obvious under §103, the present case does not present such circumstances. As noted in MPEP § 2145, an “‘obvious to try’ rationale may support a conclusion that a claim would have been obvious where one skilled in the art is choosing from *a finite number of identified, predictable solutions, with a reasonable expectation of success.*” MPEP § 2145 (citing *KSR*) (emphasis added). Applicant has shown previously that the cited references do not set forth a “finite number of identified” solutions, do not set forth “predictable” solutions, and do not provide a reasonable expectation of success. Thus, neither the MPEP nor *KSR* itself support application of the “obvious to try” standard to the present invention.

For at least the foregoing reasons, Applicant respectfully requests reconsideration and withdrawal of the §103 rejections of claims 1-3, 6-8, 10 and 11-14.

## **2. Claims 4 and 9**

Claim 4 is rejected for alleged obviousness in view of the above references and Malet (1988). Claim 9 is rejected for alleged obviousness in view of the above references and U.S. 5,613,958 (Kochinke). Applicant respectfully traverses these rejections, as neither of these secondary references remedies the inability of the primary references to teach or suggest the recited methods as a whole.

Malet is cited for teaching that the “trans” isomer of 4-OHT has stronger antiproliferative effects than the “cis” isomer. Combining Malet with the other references, however, still fails to establish a prima facie case of obviousness of the method recited in claim 4.

Kochinke is cited for teaching a composition comprising isopropyl myristate, ethanol and hydroxypropylcellulose. Combining Kochinke with the other references, however, still fails to establish a prima facie case of obviousness of the method recited in claim 9.

Thus, Applicant respectfully requests reconsideration and withdrawal of the §103 rejections of claims 4 and 9.

## **Conclusion**

Applicant believes that the application is in condition for allowance, and an early notice to that effect is earnestly solicited.

Should there be any questions regarding this application, or should any issue remain, the Examiner is invited to contact the undersigned by telephone in order to advance prosecution.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to

charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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